PCT/US93/10624

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark Office
(Box PCT)
Washington D.C. 20231
United States of America

in its capacity as elected Office

NOTIFICATION CONCERNING DOCUMENT TRANSMITTED

Date of mailing:	
28 March 1995 (28.03.95)	
International application No.: PCT/US93/10624	International filing date: 05 November 1993 (05.11.93)
Applicant: SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH et al	

The International Bureau transmits herewith the following documents and number thereof:

_____ copy of the international preliminary examination report (Article 36(3)(a))

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorised officer:
Facsimile No.: (41-22) 740.14.35	I. Britel Telephone No.: (41-22) 730.91.11

Form PCT/IB/310 (July 1992)

000701393

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
Washington, D.C.

in its capacity as elected Office

Date of mailing: 14 July 1994 (14.07.94)	
International application No.: PCT/US93/10624	Applicant's or agent's file reference: 41426-A-PCT
International filing date: 05 November 1993 (05.11.93)	Priority date: 05 November 1992 (05.11.92)
Applicant: ISRAELI, Ron, S. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

03 June 1994 (03.06.94)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

T. Zhao

Telephone No.: (41-22) 730.91.11

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

WHITE, John, P.
Cooper & Dunham
30 Rockefeller Plaza
New York, NY 10112
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year): 19 August 1994 (19.08.94)

Applicant's or agent's file reference: 41426-A-PCT

IMPORTANT NOTIFICATION

International application No.: PCT/US93/10624

International filing date (day/month/year): 05 November 1993 (05.11.93)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address

COBERT, Robert, J.
Cooper & Dunham
30 Rockefeller Plaza
New York, NY 10112
United States of America

State of Nationality | State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

WHITE, John, P.
Cooper & Dunham
30 Rockefeller Plaza
New York, NY 10112
United States of America

State of Nationality | State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary: The agent's address for correspondence has changed. All correspondence should now be addressed to the new associate agent, identified in box 2.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

J.D. Hawkins

Telephone No. (41-22) 730.91.11

Form PCT/IB/306 (July 1992)

PATENT COOPERATION TREA Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

WHITE, John, P.
Cooper & Dunham
30 Rockefeller Plaza
New York, NY 10112
ETATS-UNIS D'AMERIQUE

Date of mailing (*day/month/year*): 19 August 1994 (19.08.94)

Applicant's or agent's file reference: 41426-A-PCT

IMPORTANT NOTIFICATION

International application No.: PCT/US93/10624

International filing date (*day/month/year*): 05 November 1993 (05.11.93)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address

COBERT, Robert, J.
Cooper & Dunham
30 Rockefeller Plaza
New York, NY 10112
United States of America

State of Nationality | State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

WHITE, John, P.
Cooper & Dunham
30 Rockefeller Plaza
New York, NY 10112
United States of America

State of Nationality | State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary: The agent's address for correspondence has changed. All correspondence should now be addressed to the new associate agent, identified in box 2.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

J.D. Hawkins

Telephone No. (41-22) 730.91.11

Form PCT/IB/306 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 41426-A-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US93/10624	International filing date *(day/month/year)* 05 NOVEMBER 1993	Priority date *(day/month/year)* 05 NOVEMBER 1992
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of — sheets.

3. This report contains indications relating to the following items:

- I [X] Basis of the report
- II [ ] Priority
- III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV [X] Lack of unity of invention
- V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [X] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03 JUNE 1994	19 DECEMBER 1994
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Deborah Frieno for ANTHONY CAPUTA Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US93/10624

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

[X] the international application as originally filed.

[X] the description, pages 1-125 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____.
pages _____ , filed with the letter of _____.

[X] the claims, Nos. 1-89 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. NONE , filed with the demand.
Nos. NONE , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

[X] the drawings, sheets/~~fig~~ 1-48 , as originally filed.
sheets/~~fig~~ NONE , filed with the demand.
sheets/~~fig~~ NONE , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[X] the description, pages NONE.

[X] the claims, Nos. NONE.

[X] the drawings, sheets/~~fig~~ NONE.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US93/10624

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

Please See Supplemental Sheet.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-21, and 74-83 (Groups 1 and XII).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US93/10624

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	12, 13 15-21, and 74-83	YES
	Claims	1-11 and 14	NO
Inventive Step (IS)	Claims	12, 13, and 78-83	YES
	Claims	1-11, 14-21 and 74-77	NO
Industrial Applicability (IA)	Claims	1-21, and 74-83	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1, 4-6, 8, 9, 11, and 14 lack novelty under PCT Article 33(2) as being disclosed by Solin et al.

Solin et al. disclose isolated total RNA from LNCaP (see entire document; especially pages 72, 73 and Figure 2). It is reasonable to conclude that the isolated RNA of the prior art inherently encodes the claimed antigen, as the gene encoding the claimed antigen is derived from the same source as disclosed in the prior art. Further the RNA of the prior art is at least 15 nucleotides and capable of hybridizing with an isolated nucleic acid molecule (i.e. genomic DNA) as claimed. Since the synthesis of proteins involves RNA transcription it is inherent the antigen encoded is linked to a promoter of RNA transcription.

Claims 1-11, and 14 lack novelty under PCT Article 33(2) as being disclosed by Faber et. al. (J. Biol. Chem. 266: 10743- 10749, 6/91).

Faber et al. disclose isolated RNA and a cDNA library from LNCaP (see entire document; especially pages 10745 and 10747). It is inherent that the isolated RNA and cDNA of the prior art encodes the claimed antigen as the gene encoding the claimed antigen is derived from the same source. Further the nucleic acid molecule of the prior art is at least 15 nucleotides and capable of hybridizing with an isolated nucleic acid molecule (i.e. genomic DNA) as claimed. Further since the synthesis of proteins involves RNA transcription it is inherent the antigen encoded is linked to a promoter of RNA transcription.

Claims 1-11, and 14-21 lack an inventive step under PCT Article 33(3) as being taught over Feng et al., Lopes et al. in further view of Young et al. and Sambrook et al.

Feng et al. teach a membrane bound 100-kD glycoprotein found in LNCaP cells which is recognized by the monoclonal antibody 7E11-C5. Feng et al. teach the carbohydrate portion is involved in the recognition of the antibody. Feng et al. teach the antigen is distinct from other prostate and non-prostate tumor associated antigens.

Lopes et al. teach of an antibody CYT-356 (7E11-C5-GYK- DTPA), an immunoconjugate derived from the monoclonal antibody (Continued on Supplemental Sheet.)

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 6, 9, 12, 13, and 78-83 are objected to under PCT Article 6 because they are not fully supported by the disclosure.

The description does not fully support using primer(s) or nucleic acid molecules which specifically hybridize with the nucleic acid molecule which encodes for the mammalian prostate specific membrane antigen as claimed. The nucleotide sequence of the prostate specific membrane antigen is over 2000 nucleotides and it would be an undue burden to an artisan in the art to determine those molecule(s) of at least 15 nucleotide that specifically hybridize as claimed since it would not have been expected that each particular molecule hybridizes equivalently. Additionally it would be an undue burden to identify which molecule specifically hybridize since the description provides no guidance to the conditions used for the specific hybridization as recited.

The description provides insufficient guidance to the identity of the primers for detection as broadly claimed. It would not have been expected that all primers would have been useful and it would be an undue burden to determine which primers are specific. Additionally, the description provides insufficient evidence the primers as disclosed (see page 89-95) are useful for detection. The description provides insufficient guidance to ascertain as to whether or not the primers react with patients which do not have tumor cells (i.e. patients that are apparently cured and/or never had cancer).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(6): A61K 39/00, 39/395, 48/00; C07K 1/00, 4/12, 14/47, 14/705; C12N 15/12; C12P 19/34; C12Q 1/68; G01N 33/53, 37/00 and US Cl.: 424/85.1, 85.8, 88, 93U; 435/6, 7.1, 69.3, 91.2; 514/44; 530/350, 388.1, 389.7; 800/2, DIG1, DIG2; 935/3, 8, 12

IV. LACK OF UNITY OF INVENTION:

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2, and 13.3 is not complied with for the following reasons:

As applicant was previously notified this International Preliminary Examining Authority has found plural inventions claimed in the International Application covered by the claims indicated below:

I. Claims 1-21, and 74-77, drawn to nucleic acid molecule, vector, host cell, vaccine comprising said host cell, and method of using nucleic acid molecule for hybridization.
II. Claims 22, 23, 26-29, and 31 drawn to a ligand.
III. Claims 24 and 25 drawn to a protein.
IV. Claim 30 drawn to method of using the ligand for imaging.
V. Claims 32-38, 42, 43 drawn to a monoclonal antibody.
VI. Claims 39, 40, and 41 drawn to a method of using the antibody for imaging.
VII. Claim 44 drawn to method of using antibody in an immunoassay.
VIII. Claim 45 drawn to method of using ligand in an immunoassay.
IX. Claim 46 drawn to a method of using antibody for the purification of protein.
X. Claims 47 and 48 drawn to transgenic animal.
XI. Claims 49-73, 84-89 drawn to method of using the nucleic acid molecule for suppression of tumor cells or abrogation of a mitogenic response.
XII.Claims 78-83 drawn to method of using nucleic acid for detection by using PCR.

and it considers that the International Application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

The claims of these groups are directed to different inventions which are not linked to form a single general concept. The claims in the different groups do not have in common the same or corresponding "special technical features" under PCT Rule 13.2. In particular, Groups (I, X, XI, XII), (II, IV, VIII), (III) and (V, VI, VII, IX) are drawn to four distinct products namely nucleic acid molecule, ligands, proteins and antibodies which differ in biological properties and chemical structure. The nucleic acid is made up of nucleotides, and the ligands, protein and antibodies are made of amino acids. Antibodies differ from ligands and protein in that the antibodies structurally consists of Fab and Fc portions. Ligands differ from the claimed protein in amino acid composition and binding properties (e.g. ligands bind to protein). Further the products can be made and/or used independently from one another. Groups I, X, XI and XII are distinct from one another since each method of using the nucleic acid molecule is completely different which require different parameters and reagents. Further, groups (I or X), XI and XII each have a different use of the nucleic acid molecule (i.e. detection, suppression or production of protein). Group II drawn to the ligand is distinct from Groups IV and VIII drawn to methods of using the ligand since the ligand can be used for different uses (i.e. IV or VIII). Further, groups IV and VIII drawn to distinct methods of using the ligands arecompletelydifferent which require different parameters and reagents. Group IV and VIII each have a different use of the ligand (i.e. imaging or immunoassays). Group V drawn to the antibody is distinct from Groups VI, VII, and IX since the antibody can be used for different uses (i.e. VI, VII, or IX). Further Groups VI, VII, and IX drawn to distinct method of using the antibody are completely different which require different parameters and reagents. Group VI, VII, and IX each have a different use of the antibody (i.e. imaging, immunoassay, and purification).

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
7E11-C5 that may be useful for diagnosis and therapy of prostate cancer. Lopes et al. teach the antigen recognized by the monoclonal antibody 7E11-C5 has a molecular weight of 100,000.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Feng et al. nor Lopes et al. teach of cloning the antigen.

Young and Davis teach of an isolating genes and detecting the antigen by using antibody probes. Young and Davis teach of an expression vector that permits the construction and maintenance of large cDNA libraries, of the production of a fusion protein that minimizes the degradation of foreign proteins (e.g. eucaryotic proteins), and host cells that are defective in protein degradation pathways.

Sambrook (see page 16.3) teach expressing proteins using eucaryotic vectors since post translational modifications, such as glycosylation, processing and assembly are unlikely to be carried out by *E. coli*.

Since the antigen is glycosylated it would have been obvious to one of ordinary skill in the art to clone the protein in a eucaryotic vector which expresses and modifies the protein as the native protein as disclosed by Sambrook with the monoclonal antibody as disclosed by Feng et al. or Lopes et al. or in the alternative use polyclonal antibody to the purified protein as described by Feng et al. and Lopes et al. to screen for the production of the antigen by the method as described by Young and Davis or by Sambrook since the monoclonal antibody as described by Feng et al. recognizes the carbohydrate moiety of the 100 kDa antigen.

It would have been obvious to one of ordinary skill in the art at the time of the invention to clone and express the antigen by the method described by Young and Davis (see page 1198) since it is easily purified (i.e. produced in large amounts and fused to beta galactosidase). Since the synthesis of proteins involves RNA transcription it would have been expected that the antigen encoded is linked to a promoter of RNA transcription. Since the monoclonal antibody recognized by the antigen appears to be useful for therapy of prostate cancer as set forth by Lopes et al. it would have been obvious and expected to one of ordinary skill in the art that the 100-kD glycoprotein found in LNCaP cells or the prostate cells as described by Feng et al. would have been useful as a vaccine. Since the cells express the 100 kda protein it would have been expected that said cells would contain the DNA, and the regulatory regions (i.e. promoter, enhancer) for expressing said protein

Sambrook et al. (see Chapter 16, especially pages 16.3, 16.5, 16.17, 16.18, 16.19, and 16.68-16.72) teach of expressing proteins using eucaryotic vectors in mammalian and insect cells since post translational modifications, such as glycosylation, processing and assembly are unlikely to be carried out by *E. coli*. Sambrook et al. teach the expression in mammalian cells can be identified immunologically (see page 16.68-16.72). Sambrook et al. further teach that the SV40 vectors contain the promoters for transcription (see pages 16.17 and 16.18) and most eucaryotic expression vectors contain a promoter for the control of transcription of foreign genes (see page 16.5). Since the antigen is glycosylated as disclosed by Feng et al. it would have been obvious to one of ordinary skill in the art to clone the protein as disclosed by Feng et al. and/or Lopes et al. in a eucaryotic vector which expresses and modifies the protein as the native protein as disclosed by Sambrook et al. It would have been expected that the recombinant protein would have the biological activity of the native antigen. For the reasons described above it would have been expected that the isolated DNA or RNA of the instant application and the prior art would have been a functional equivalent. Further it would have been expected that the vector(s) of the prior art would have been a functional equivalent to the claimed vectors of the instant application.

It would have been further obvious to determine the DNA sequence of the DNA fragment that encodes the protein and use DNA fragments of the gene not known to be homologous to other known sequences in the art to obtain those fragment which specifically hybridize to the gene (nucleic acid molecule) encoding the antigen as disclosed by Lopes et al. and Feng et al.

---------- NEW CITATIONS ----------

NONE

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 41426-A-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US93/10624	International filing date *(day/month/year)* 05 NOVEMBER 1993	Priority date *(day/month/year)* 05 NOVEMBER 1992
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of — sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☒ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☒ Certain observations on the international application

Date of submission of the demand 03 JUNE 1994	Date of completion of this report 19 DECEMBER 1994
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Deborah Frieze for ANTHONY CAPUTA Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (January 1994)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US93/10624

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

[X] the international application as originally filed.

[X] the description, pages 1-125 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____.
pages _____ , filed with the letter of _____.

[X] the claims, Nos. 1-89 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. NONE , filed with the demand.
Nos. NONE , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

[X] the drawings, sheets/~~fig~~ 1-48 , as originally filed.
sheets/~~fig~~ NONE , filed with the demand.
sheets/~~fig~~ NONE , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[X] the description, pages NONE.

[X] the claims, Nos. NONE.

[X] the drawings, sheets/~~fig~~ NONE.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:
NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US93/10624

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

Please See Supplemental Sheet.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-21, and 74-83 (Groups 1 and XII).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US93/10624

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	12, 13 15-21, and 74-83	YES
	Claims	1-11 and 14	NO
Inventive Step (IS)	Claims	12, 13, and 78-83	YES
	Claims	1-11, 14-21 and 74-77	NO
Industrial Applicability (IA)	Claims	1-21, and 74-83	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1, 4-6, 8, 9, 11, and 14 lack novelty under PCT Article 33(2) as being disclosed by Solin et al.

Solin et al. disclose isolated total RNA from LNCaP (see entire document; especially pages 72, 73 and Figure 2). It is reasonable to conclude that the isolated RNA of the prior art inherently encodes the claimed antigen, as the gene encoding the claimed antigen is derived from the same source as disclosed in the prior art. Further the RNA of the prior art is at least 15 nucleotides and capable of hybridizing with an isolated nucleic acid molecule (i.e. genomic DNA) as claimed. Since the synthesis of proteins involves RNA transcription it is inherent the antigen encoded is linked to a promoter of RNA transcription.

Applicants assert that Solin et al. does not disclose the nucleic acid molecule which encodes the mammalian specific antigen. Applicants argue that Solin et al. teaches of the expression of PAP mRNA. Applicants arguments are not persuasive.

While it is true that Solin et al, disclose the expression of PAP mRNA as asserted by applicants, since Solin et al. disclose isolated total RNA from LNCaP, as set forth in the description it is inherent that the isolated RNA of the prior art encodes the claimed antigen, since the gene encoding the claimed antigen is derived from the same source as described in the prior art. It is the Examiner's position that the prior art disclose a nucleic molecule (RNA) which encodes for the prostate specific antigen and arguments as to the establishment of where to find the specific sequence does not impart novelty to the claim. Further, applicants lack of using closed language to claim a nucleic molecule which encodes the prostate specific membrane antigen as claimed leaves the claim open for inclusion of unspecified ingredients, even in large amounts.

Claims 1-11, and 14 lack novelty under PCT Article 33(2) as being disclosed by Faber et. al. (J. Biol. Chem. 266: 10743- 10749, 6/91).

Faber et al. disclose isolated RNA and a cDNA library from LNCaP (see entire document; especially pages 10745 and 10747). It is inherent that the isolated RNA and cDNA of the prior art (Continued on Supplemental Sheet.)

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 6, 9, 12, 13, and 78-83 are objected to under PCT Article 6 because they are not fully supported by the disclosure.

The description does not fully support using primer(s) or nucleic acid molecules which specifically hybridize with the nucleic acid molecule which encodes for the mammalian prostate specific membrane antigen as claimed. The nucleotide sequence of the prostate specific membrane antigen is over 2000 nucleotides and it would be an undue burden to an artisan in the art to determine those molecule(s) of at least 15 nucleotide that specifically hybridize as claimed since it would not have been expected that each particular molecule hybridizes equivalently. Additionally it would be an undue burden to identify which molecule specifically hybridize since the description provides no guidance to the conditions used for the specific hybridization as recited.

The description provides insufficient guidance to the identity of the primers for detection as broadly claimed. It would not have been expected that all primers would have been useful and it would be an undue burden to determine which primers are specific. Additionally, the description provides insufficient evidence the primers as disclosed (see page 89-95) are useful for detection. The description provides insufficient guidance to ascertain as to whether or not the primers react with patients which do not have tumor cells (i.e. patients that are apparently cured and/or never had cancer).

Applicants maintain the description provides sufficient guidance to the identity of nucleic acid molecules of at least 15 molecules that specifically hybridize to the nucleic acid molecule encoding the prostate specific antigen. Applicants assert the description exemplifies that varying lengths may be employed for hybridization and the experimental conditions for hybridization (see pages 16-19). Applicants arguments are not persuasive since there is no guidance of the conditions used for hybridization. For instance, the description does not disclose the experimental parameters used for hybridization on pages 16-19. Accordingly, it is the Examiner's position that it would be an undue burden to identify nucleic acid of at least 15 nucleotide which specifically hybridize to the nucleic acid molecule encoding the specific antigen.

Applicants further assert the protocols for hybridization using nucleic acid probes which include experimental conditions are known to those ordinary skilled in the art, as set forth by Sambrook who define the hybridization conditions. Applicants arguments are not sufficient to overcome the art since: 1.) the teachings of Sambrook (pages 1.101-1.104) are not provided by applicants to determine whether or not it establishes the (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(6): A61K 39/00, 39/395, 48/00; C07K 1/00, 4/12, 14/47, 14/705; C12N 15/12; C12P 19/34; C12Q 1/68; G01N 33/53, 37/00 and US Cl.: 424/85.1, 85.8, 88, 93U; 435/6, 7.1, 69.3, 91.2; 514/44; 530/350, 388.1, 389.7; 800/2, DIG1, DIG2; 935/3, 8, 12

IV. LACK OF UNITY OF INVENTION:

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2, and 13.3 is not complied with for the following reasons:
As applicant was previously notified this International Preliminary Examining Authority has found plural inventions claimed in the International Application covered by the claims indicated below:

I. Claims 1-21, and 74-77, drawn to nucleic acid molecule, vector, host cell, vaccine comprising said host cell, and method of using nucleic acid molecule for hybridization.
II. Claims 22, 23, 26-29, and 31 drawn to a ligand.
III. Claims 24 and 25 drawn to a protein.
IV. Claim 30 drawn to method of using the ligand for imaging.
V. Claims 32-38, 42, 43 drawn to a monoclonal antibody.
VI. Claims 39, 40, and 41 drawn to a method of using the antibody for imaging.
VII. Claim 44 drawn to method of using antibody in an immunoassay.
VIII. Claim 45 drawn to method of using ligand in an immunoassay.
IX. Claim 46 drawn to a method of using antibody for the purification of protein.
X. Claims 47 and 48 drawn to transgenic animal.
XI. Claims 49-73, 84-89 drawn to method of using the nucleic acid molecule for suppression of tumor cells or abrogation of a mitogenic response.
XII.Claims 78-83 drawn to method of using nucleic acid for detection by using PCR.

and it considers that the International Application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

The claims of these groups are directed to different inventions which are not linked to form a single general concept. The claims in the different groups do not have in common the same or corresponding "special technical features" under PCT Rule 13.2. In particular, Groups (I, X, XI, XII), (II, IV, VIII), (III) and (V, VI, VII, IX) are drawn to four distinct products namely nucleic acid molecule, ligands, proteins and antibodies which differ in biological properties and chemical structure. The nucleic acid is made up of nucleotides, and the ligands, protein and antibodies are made of amino acids. Antibodies differ from ligands and protein in that the antibodies structurally consists of Fab and Fc portions. Ligands differ from the claimed protein in amino acid composition and binding properties (e.g. ligands bind to protein). Further the products can be made and/or used independently from one another. Groups I, X, XI and XII are distinct from one another since each method of using the nucleic acid molecule is completely different which require different parameters and reagents. Further, groups (I or X), XI and XII each have a different use of the nucleic acid molecule (i.e. detection, suppression or production of protein). Group II drawn to the ligand is distinct from Groups IV and VIII drawn to methods of using the ligand since the ligand can be used for different uses (i.e. IV or VIII). Further, groups IV and VIII drawn to distinct methods of using the ligands arecompletelydifferent which require different parameters and reagents. Group IV and VIII each have a different use of the ligand (i.e. imaging or immunoassays). Group V drawn to the antibody is distinct from Groups VI, VII, and IX since the antibody can be used for different uses (i.e. VI, VII, or IX). Further Groups VI, VII, and IX drawn to distinct method of using the antibody are completely different which require different parameters and reagents. Group VI, VII, and IX each have a different use of the antibody (i.e. imaging, immunoassay, and purification).

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
encodes the claimed antigen as the gene encoding the claimed antigen is derived from the same source. Further the nucleic acid molecule of the prior art is at least 15 nucleotides and capable of hybridizing with an isolated

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

nucleic acid molecule (i.e. genomic DNA) as claimed. Further since the synthesis of proteins involves RNA transcription it is inherent the antigen encoded is linked to a promoter of RNA transcription.

Applicants arguments are essentially the same as set forth above for the claimed invention lacking novelty over the disclosure of Solin et al. For the reasons stated above it is maintained that the claims lack novelty over the disclosure of Faber et al.

Claims 1-11, and 14-21 lack an inventive step under PCT Article 33(3) as being taught over Feng et al., Lopes et al. in further view of Young et al. and Sambrook et al.

Feng et al. teach a membrane bound 100 kDa glycoprotein found in LNCaP cells which is recognized by the monoclonal antibody 7E11-C5. Feng et al. teach the carbohydrate portion is involved in the recognition of the antibody. Feng et al. teach the antigen is distinct from other prostate and non-prostate tumor associated antigens.

Lopes et al. teach of an antibody CYT-356 (7E11-C5-GYK- DTPA), an immunoconjugate derived from the monoclonal antibody 7E11-C5 that may be useful for diagnosis and therapy of prostate cancer. Lopes et al. teach the antigen recognized by the monoclonal antibody 7E11-C5 has a molecular weight of 100,000.

Feng et al. nor Lopes et al. teach of cloning the antigen.

Young and Davis teach of an isolating genes and detecting the antigen by using antibody probes. Young and Davis teach of an expression vector that permits the construction and maintenance of large cDNA libraries, of the production of a fusion protein that minimizes the degradation of foreign proteins (e.g. eucaryotic proteins), and host cells that are defective in protein degradation pathways.

Sambrook (see page 16.3) teach expressing proteins using eucaryotic vectors since post translational modifications, such as glycosylation, processing and assembly are unlikely to be carried out by *E. coli*.

Since the antigen is glycosylated it would have been obvious to one of ordinary skill in the art to clone the protein in a eucaryotic vector which expresses and modifies the protein as the native protein as disclosed by Sambrook with the monoclonal antibody as disclosed by Feng et al. or Lopes et al. or in the alternative use polyclonal antibody to the purified protein as described by Feng et al. and Lopes et al. to screen for the production of the antigen by the method as described by Young and Davis or by Sambrook since the monoclonal antibody as described by Feng et al. recognizes the carbohydrate moiety of the 100 kDa antigen.

It would have been obvious to one of ordinary skill in the art at the time of the invention to clone and express the antigen by the method described by Young and Davis (see page 1198) since it is easily purified (i.e. produced in large amounts and fused to beta galactosidase). Since the synthesis of proteins involves RNA transcription it would have been expected that the antigen encoded is linked to a promoter of RNA transcription. Since the monoclonal antibody recognized by the antigen appears to be useful for therapy of prostate cancer as set forth by Lopes et al. it would have been obvious and expected to one of ordinary skill in the art that the 100 kDa glycoprotein found in LNCaP cells or the prostate cells as described by Feng et al. would have been useful as a vaccine. Since the cells express the 100 kda protein it would have been expected that said cells would contain the DNA, and the regulatory regions (i.e. promoter, enhancer) for expressing said protein.

Sambrook et al. (see Chapter 16, especially pages 16.3, 16.5, 16.17, 16.18, 16.19, and 16.68-16.72) teach of expressing proteins using eucaryotic vectors in mammalian and insect cells since post translational modifications, such as glycosylation, processing and assembly are unlikely to be carried out by *E. coli*. Sambrook et al. teach the expression in mammalian cells can be identified immunologically (see page 16.68-16.72). Sambrook et al. further teach that the SV40 vectors contain the promoters for transcription (see pages 16.17 and 16.18) and most eucaryotic expression vectors contain a promoter for the control of transcription of foreign genes (see page 16.5). Since the antigen is glycosylated as disclosed by Feng et al. it would have been obvious to one of ordinary skill in the art to clone the protein as disclosed by Feng et al. and/or Lopes et al. in a eucaryotic vector which expresses and modifies the protein as the native protein as disclosed by Sambrook et al. It would have been expected that the recombinant protein would have the biological activity of the native antigen. For the reasons described above it would have been expected that the isolated DNA, RNA and vector of the instant application and the prior art would have been a functional equivalent.

It would have been further obvious to one of ordinary skill in the art to determine the DNA sequence of the DNA fragment that encodes the protein and use DNA fragments of the gene not known to be homologous to other known sequences in the art to obtain those fragment which specifically hybridize to the gene (nucleic acid molecule) encoding the antigen as disclosed by Lopes et al. and Feng et al.

Applicants assert the authors of Feng et al. have been unable to produce the isolated nucleic acid molecule encoding a prostate specific membrane antigen. Applicants arguments are not persuasive since applicants provide no evidence as to why the authors of Feng et al. have been unable to produce the nucleic acid molecule as claimed. It is not clear from applicants arguments if Feng or other artisans in the art attempted to screen for

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

the production of the 100 kDa antigen with the monoclonal antibody in a eucaryotic vector; and/or polyclonal antibody in a eucaryotic or procaryotic vector using the method as taught by Young et al. or Sambrook et al. It is the Examiner's position that in view of the teachings of Feng, Lopes, Young and Davis and Sambrook one of ordinary skill in the art would have been motivated and expected to obtain a host which expresses the 100 kDa, and the nucleic acid molecule encoding said antigen.

Applicants argue to employ a polyclonal antibody to the protein as described by Feng et al. and Lopes et al. for the production of an antigen using the method as set forth by Young and Davis is not obvious. Applicants arguments are not persuasive. Applicants arguments are only conclusionary. As stated previously Young and Davis teach isolating genes and detecting the antigen by using polyclonal antibody probes.

Applicants further contend that a monoclonal antibody to 7 E11-C5 would not used in the method by Young and Davis. Applicant arguments are noted. However, in view that the rejection of the teachings of Young and Davis is over the use of polyclonal antibody, applicants arguments are moot.

Applicants further argue that since 7E11-C5 or CYT-356 is non-specific that one of ordinary skill in the art would not have used said antibody. Applicants arguments are not persuasive since Lopes et al. teach that no reactivity of the monoclonal antibody 7E11-C5 was seen with a panel of 10 other tumor types. Further, in contrast to most other prostate monoclonal antibody, CYT-356 a immunoconjugate of 7E11-C5 selectively reacts (see Lopes et al. page 6428). Lopes et al. teach the cross reactivity of the monoclonal antibody is probably due to the fixation of the tissue and the monoclonal antibody is useful for diagnosis. Accordingly, it is the Examiner's position that one of ordinary skill in the art would have expected the monoclonal antibody to be specific since Lopes et al. teach of no reactivity with other tumors, it use for diagnosis and the reaction with skeletal muscle was due to the fixation techniques, a technique which was not taught in the methods of Young et al. or Sambrook. Further, with regards to the reaction with other tissue types, it would not have been expected that said reaction be a problem since one of ordinary skill in the art would not have used cardiac muscle as a tissue source for cloning since the antigen that react with the monoclonal antibody is associated with prostate tumors as taught in the prior art. Applicants citation of Israeli et al. 1994 to demonstrate the monoclonal antibody is not specific is noted. However, since said reference was not provided by applicants the reference by Israeli et al. can not be considered on it merits.

---------- NEW CITATIONS ----------
NONE

VIII. CERTAIN OBSERVATIONS ON THE APPLICATION (Continued):

experimental conditions needed to define the specific hybridization conditions 2.) the specification does not teach of using the particular teachings of prior art cited (e.g. Sambrook) to define the conditions as claimed and; 3.) experimental conditions as concentrations as salt, temperature, stringency and others factors that define specific hybridization of DNA are not set forth in the specification. For the reasons stated above applicants arguments are not persuasive.

PCT/US93/10624

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classificati n (IPC) r to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/85.1, 85.8, 88, 93U; 435/6, 7.1, 69.3, 91.2; 514/44; 530/350, 388.1, 389.7; 800/2, DIG1, DIG2; 935/3, 8, 12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	BIOCHIMICA ET BIOPHYSICA ACTA, Volume 1048, issued 1990, T. Solin et al., "Gene Expression and Prostate Specificity of Human Prostatic Acid Phosphatase (PAP): Evaluation by RNA Blot Analyses", pages 72-77, see entire document.	1,4-6,8-9,11,14 12, 13
X	JOURNAL OF BIOLOGICAL CHEMISTRY, Volume 266, Number 17, issued 15 June 1991, P.W. Faber et al., "Characterization of the Human Androgen Receptor Transcription Unit", pages 10743-10749, see entire document.	1-11, 14

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 DECEMBER 1993	Date of mailing of the international search report 27 JAN 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer ANTHONY C. CAPUTA Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	PROCEEDINGS OF THE 82ND ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, Volume 32, issued March 1991, Q. Feng et al., "Purification and Biochemical Characterization of the 7E11-C5 Prostate Carcinoma-Associated Antigen", page 239, see abstract.	24, 25, 34, 36 1-23,26-33,35,37-89
X Y	CANCER RESEARCH, Volume 50, issued 01 October 1991, A.D. Lopes et al., "Immunohistochemical and Pharmacokinetic Characterization of the Site-Specific Immunoconjugate CYT-356 Derived from Antiprostate Monoclonal Antibody 7E11-C5", pages 6423-6429, see entire document.	34, 36, 44 1-33, 35, 37-43, 45-89
Y	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, Volume 80, issued March 1983, R.A. Young et al., "Efficient Isolation of Genes by Using Antibody Probes", pages 1194-1198, see entire document.	1-20, 47-89
Y	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, Volume 88, issued September 1991, B.E. Huber et al., "Retroviral-Mediated Gene Therapy for the Treatment of Hepatocellular Carcinoma: An Innovative Approach For Cancer Therapy", pages 8039-8043, see entire document.	47-77, 80-89
Y	CANCER RESEARCH Volume 51, issued 15 March 1991, T. Mukhopadhyay et al., "Specific Inhibition of K-ras Expression and Tumorigenicity of Lung Cancer Cells by Antisense RNA, pages 1744-1748, see entire document.	47, 48
Y	EUROPEAN JOURNAL OF CANCER, Volume 27, Number 1, issued 1991, M.F. Fey et al., "The Polymerase Chain Reaction: A New Tool for the Detection of Minimal Residual Disease in Hematological Malignancies", pages 89-94, see entire document.	78, 79
Y	US, A, 4,554,101 (HOPP) 19 November 1985, see entire document.	35-38
Y	SCIENCE, Volume 256, issued 12 June 1992, K.W. Culver et al., "In Vivo Gene Transfer with Retroviral Vector-Producer Cells for Treatment of Experimental Brain Tumors", pages 1550-1552, see entire document.	47-77, 80-89

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	G.J. Tortora et al., "MICROBIOLOGY, AN INTRODUCTION", published 1989 by BENJAMIN/CUMMINGS PUBLISHING CO., INC. (CALIFORNIA), pages 423-426, and 471, see entire document.	28, 29, 32, 33, 35-38
Y	D.P. STITES et al., "BASIC AND CLINICAL IMMUNOLOGY", published 1991 by APPLETON & LANGE (CONNECTICUT), pages 229-251, see entire document.	22, 23, 26-31, 39-43
Y	N.R. ROSE et al., "MANUAL OF CLINICAL LABORATORY IMMUNOLOGY", published 1986 by AMERICAN SOCIETY FOR MICROBIOLOGY (D.C.), pages 88-109, see entire document.	44, 45
Y	W.E. PAUL, "FUNDAMENTAL IMMUNOLOGY", published 1989 by RAVEN PRESS (N.Y.), pages 628, 629, and 647-651, see entire document.	70, 71
Y	J. SAMBROOK et al., "MOLECULAR CLONING, A LABORATORY MANUAL", published 1989 by COLD SPRING HARBOR LABORATORY PRESS (N.Y.), pages 16.1-16.81, see entire document.	1-21, 47-89
P,Y	CANCER RESEARCH, Volume 53, issued 01 March 1993, R.G. Vile et al., "In Vitro and in Vivo Targeting of Gene Expression to Melanoma Cells", pages 962-967, see entire document.	47-77, 80-89
Y	JOURNAL OF UROLOGY, Volume 143, issued February 1990, H.N. Keer et al., "Elevated Transferrin Receptor Content in Human Prostate Cancer Cell Lines Assessed in Vitro and in Vivo", pages 381-385, see entire document.	84-89
Y	CELLULAR IMMUNOLOGY, Volume 143, Number 1, issued August 1992, M.K. Gately et al., "Regulation of Human Cytolytic Lymphocyte Responses by Interleukin-12", pages 127-142, see entire document.	68, 69
Y	EUROPEAN JOURNAL OF CANCER, Volume 27, Number 9, issued 1991, A. Decensi et al., "Phase II Study of the Pure Non-steroidal Antiandrogen Nilutamide in Prostatic Cancer", pages 1100-1104, see entire document.	81

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/10624

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (5):

A61K 39/00, 39/395, 48/00; C07K 3/12, 15/06, 15/28; C12N 15/12; C12P 19/34; C12Q 1/68; G01N 33/53, 37/00

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/85.1, 85.8, 88, 93U; 435/6, 7.1, 69.3, 91.2; 514/44; 530/350, 388.1, 389.7; 800/2, DIG1, DIG2; 935/3, 8, 12

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

CA, BIOSIS, EMBASE, MEDLINE, PASCAL, DERWENT WORLD PATENTS INDEX, DERWENT BIOTECHNOLOGY ABS, CURRENT BIOTECHNOLOGY ABS, APS
SEARCH TERMS: PROSTATE, MEMBRANE, ANTIGEN, PSM, 100, ISRAELI, HESTON, FAIR, androgen, IL-12, interleukin 12